

2004

Birth weight as a risk factor for autism spectrum disorders : a pilot study and case-control study

Virginia Grace Cohen
Yale University

Follow this and additional works at: <http://elischolar.library.yale.edu/ymtdl>



Part of the [Medicine and Health Sciences Commons](#)

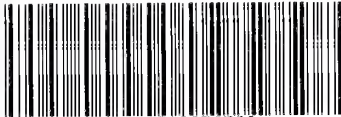
Recommended Citation

Cohen, Virginia Grace, "Birth weight as a risk factor for autism spectrum disorders : a pilot study and case-control study" (2004). *Yale Medicine Thesis Digital Library*. 2479.
<http://elischolar.library.yale.edu/ymtdl/2479>

This Open Access Thesis is brought to you for free and open access by the School of Medicine at EliScholar – A Digital Platform for Scholarly Publishing at Yale. It has been accepted for inclusion in Yale Medicine Thesis Digital Library by an authorized administrator of EliScholar – A Digital Platform for Scholarly Publishing at Yale. For more information, please contact elischolar@yale.edu.

MED
T113
+Y12
7082

YALE UNIVERSITY LIBRARY



39002010656529

PERINATAL WEIGHT AS A RISK FACTOR FOR AUTISM SPECTRUM
DISORDERS: A PILOT STUDY AND CASE-CONTROL STUDY

Virginia Grace James Cohen

YALE UNIVERSITY

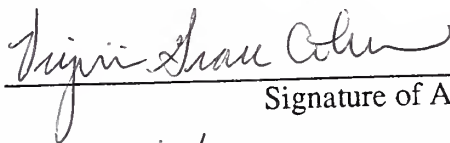
2004

YALE
UNIVERSITY



CUSHING/WHITNEY
MEDICAL LIBRARY


Permission to photocopy or microfilm processing of this thesis for the purpose of individual scholarly consultation or reference is hereby granted by the author. This permission is not to be interpreted as affecting publication of this work or otherwise placing it in the public domain, and the author reserves all rights of ownership guaranteed under common law protection of unpublished manuscripts.



Signature of Author

3/9/04

Date



Digitized by the Internet Archive
in 2017 with funding from
The National Endowment for the Humanities and the Arcadia Fund

<https://archive.org/details/birthweightasris00cohe>

**BIRTH WEIGHT AS A RISK FACTOR FOR AUTISM SPECTRUM
DISORDERS: A PILOT STUDY AND CASE-CONTROL STUDY**

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Virginia Grace James Cohen
2004

YALE MEDICAL LIBRARY

AUG 23 2004

T 113
+ Y 12
7082

BIRTH WEIGHT AS A RISK FACTOR FOR AUTISM SPECTRUM DISORDERS: A PILOT STUDY AND CASE-CONTROL STUDY.

Virginia Grace Cohen; Myriam Peralta-Carcelen and Crayton Fargason (Department of Pediatrics, University of Alabama School of Medicine); Fred Volkmar (Child Study Center, Yale University School of Medicine)

The role of birth weight and perinatal adversity in the development of autism spectrum disorders (ASDs) remains controversial. Our objective was to clarify the relationship between ASDs and low birth weight, with particular focus on the effects of extremely low birth weight (ELBW). In part one of this study, we tested a cohort of ELBW children ages 3-7 for ASDs using the Autism Diagnostic Observation Schedule (ADOS) as our primary assessment tool, and the Autism Behavior Checklist, Autism Screening Questionnaire, and the Vineland Adaptive Behavior Scales as secondary tests. Of 19 ELBW participants, 3 had ADOS total scores in the ASD or autism range; one of the three scored in the ASD range on all tests administered. In addition, 7 had abnormal scores on the ADOS communication domain, and 4 on the social interaction domain. In part two, we conducted a case-control study to look at birth weight and perinatal adversity in children with autism or pervasive developmental disorder vs. controls. In this portion of the study (n=296), mean birth weight was not significantly different among the autism, PDD, and control groups ($p=0.523$). In those with $IQ < 70$, there was a noticeable but nonsignificant trend toward higher birth weight in the autism group ($p=0.132$). There were no differences in specific adverse perinatal factors among groups. While our data suggest that low birth weight and perinatal adversity are not major risk factors for ASDs, more research is necessary to determine whether the small subgroup of ELBW children may have a tendency to develop autism-like behavioral derangements.

Acknowledgments

I would like to thank my advisor, Dr. Fred Volkmar, for his invaluable help and support, especially with the long-distance aspects of this project. I am also indebted to Dr. Myriam Peralta-Carcelen and Dr. Crayton Fargason at the University of Alabama at Birmingham for their guidance and for giving me such a wonderful opportunity to work with ELBW children and their families. Thanks also to Kirsten Bailey, Kara Snead, Leslie Harrington, Denise Coston, and others at UAB for their help with the ELBW and autism project.

My husband, family, and friends have heard more than they ever wanted to know about autism, and have been wonderful listeners and supporters throughout this process – thank you!

This research was funded in part by stipends from the Office of Student Research at Yale University School of Medicine and from the University of Alabama at Birmingham.

Table of Contents

Abstract

Acknowledgments

Introduction 1

Statement of Purpose 9

Methods 10

Results 17

Discussion 28

References 35

Appendices 42

Introduction

Since autism was first described by Leo Kanner in 1943, the etiology of this mysterious disorder has fascinated both the medical community and the general public. Interest has been sparked in recent years by what appears to be a significant increase in the prevalence of autism spectrum disorders, a puzzling phenomenon that has not yet been fully explained. As the number of American children with autism and related conditions has grown, so has recognition of the critical importance of research into this field; in the fall of 2003, the federal government launched a long-term initiative aimed at promoting biomedical research, establishing better screening and diagnostic tools, and formulating more effective therapies for autistic disorders (1). In this climate, defining and understanding the risk factors for autism is a necessary step in early diagnosis and, ultimately, prevention of the disorder.

Autism is characterized by qualitative deficits in communication and reciprocal social interaction, and by repetitive or stereotyped behaviors and interests (see Appendix A for full diagnostic criteria [2]). Onset occurs in early childhood, usually before age three. Autism is frequently marked by language delay and impoverished imagination, and is more likely to affect boys than girls (3). Intellectual function is impaired in approximately 75% of children with autism; one recent meta-analysis (4) demonstrated that 23.5% of autistic subjects were without intellectual impairment, 22.3% had mild to moderate impairment (IQ 35-70), and 54.9% had a severe to profound level of mental retardation (IQ <35). Autism spectrum disorder (ASD), synonymous with pervasive developmental disorder (PDD), is an umbrella term that encompasses a variety of related disorders -- such as Asperger syndrome, PDD not otherwise specified (PDD-NOS)),

atypical autism, and autism itself -- that span a continuum of social and communication deficits.

The incidence and prevalence of ASDs are somewhat controversial, with prevalence estimates increasing dramatically over the last decade. Recent meta-analyses (5,6) of epidemiological studies conservatively estimate the prevalence of autism to be about 10 per 10,000 (up from estimates of 2-5 per 10,000 in the 1970s) and the prevalence of ASDs to fall between 20 and 50 per 10,000. One of the more recent prevalence studies (7), published in June of 2001, found a rate of 16.8 per 10,000 for autistic disorder and 62.6 per 10,000 for ASDs, inclusive of autism. Other research (8-10) has yielded even higher numbers: 21-40 per 10,000 for autism and 58-67 per 10,000 for all ASDs combined. At present, it is not known whether these growing numbers reflect changing diagnostic definitions of autism and ASDs, heightened awareness among healthcare professionals and the public, a true rise in incidence, or some combination of these factors. Data from the Minnesota public school system (11) suggests that while autism rates have been rising, there have been no decreases in other categories of educational disability to suggest diagnostic substitution as the sole explanation for the increasing ASD rates. Regardless of the reason for the rise, however, disorders of this type have become a significant and fairly common pediatric concern.

Autism spectrum disorders are generally thought to result from a complex interplay between genetics and neurobiological factors, likely occurring when environmental influences act on a genetically susceptible individual (12,13). The precise etiology is unknown in most cases, but an underlying disorder or aberration can be pinpointed in a minority of individuals with an ASD (14). Twin and family studies, as

well as molecular and cytogenetic research, have established a strong genetic component to autism (15-17). Concordance rates are much higher for monozygotic twins (80-90%) than for dizygotic (9-30% [18-20]). The reported rate of autism among siblings ranges from 2-7%, with siblings of autistic patients 50-200 times more likely to have autism than members of the general population (21-22, 13). The genetics of autism are certainly complex, likely involving multiple genes that have yet to be identified.

Associations have been demonstrated between autism and tuberous sclerosis, neurofibromatosis, fragile X syndrome, and seizure disorders (23-26). Congenital infections, lead poisoning, metabolic diseases, brain lesions, and neurochemical abnormalities may also be associated with autism, although the evidence for these is relatively weak (27). (Of note, several recent studies [28,29] have failed to find any association between the measles, mumps, and rubella [MMR] vaccine and the development of autism.) Overall, the rate of concurrence between autism and known medical conditions is estimated to be about 10-25% (30,31).

Courchesne and colleagues (32) have recently demonstrated that reduced head size at birth, followed at 6-14 months of age by an abnormally accelerated pattern of brain and head growth, is associated with autism spectrum disorders. The authors of this paper, who noted the unusual growth trajectory in 59% of children with an ASD compared to 6% of normal children, have speculated that abnormal brain expansion creates “noise” that may limit a child’s ability to learn about and interact with the outside world, and a critical window of time in development may be irretrievably lost. Other neurologic studies (33,34) have revealed patterns of limbic and cerebellar abnormalities in the brains of some autistic patients.

Because most cases of autism are idiopathic, further investigation into the causes and risk factors of the disorder is essential. Some researchers, mindful of the link between neurologic insults and autism, have hypothesized that obstetrical complications may be a risk factor for the disorder. In 1980, Deykin and MacMahon (35) found that autistic children were more likely than their nonautistic siblings to have experienced at least one adverse event in the pre-, peri-, or neonatal phase. The authors concluded that general physical damage resulting from unfavorable events might lead to the development of autism, but that no single complication could be named responsible. Several later studies (36-38) have provided further support for the notion that nonspecific pre-, peri-, or neonatal factors may contribute to autism, although a consistent pattern of risk factors has not been demonstrated. A wide variety of conditions and complications including maternal medication use, maternal smoking, increased paternal age, intrauterine stress, abnormal presentation at delivery, decreased birth weight, and hyperbilirubinemia have been implicated in the last few years with the later development of an ASD (39-42).

Other studies, however, have called these findings into question. Piven, et al. (43) found that adjusting for birth order eliminated apparent differences in obstetrical optimality between autistic children and their siblings. Another study of 49 autistic children (44) found no difference in maternal age, maternal parity, birth order, or low birth weight between the autistic children and controls. Two additional groups have failed to find a relationship either between specific pathologic factors or groups of factors and autism (45) or between general suboptimality and autism (46).

Taken as a whole, research into the relationship between autism and obstetric or perinatal adversity is inconclusive and merits further study. Even those studies that have

found a link between adverse conditions and autism disagree as to precisely which conditions are to blame, and it is difficult to find among the potential risk factors any unifying features that would suggest pathogenesis. Most existing studies document the risk of developing autism, but do not address disorders within the broader autism spectrum such as PDD-NOS. Furthermore, no one has yet considered the effects of extremely low birth weight, as opposed to low birth weight in general, on the development of autistic behaviors.

As medical advances such as surfactant and maternal steroid use have improved survival for infants of low birth weight and gestational age, a new cohort of extremely low birth weight (ELBW) children has arisen. Traditionally, low birth weight children have been stratified into three categories: low birth weight (<2500g), very low birth weight (<1500g), and extremely low birth weight (<1000g). In 2000, according to a report by the Center for Disease Control and Prevention, 7.6% of infants born were low birth weight (LBW), and 1.5% were very low birth weight (VLBW). A much smaller proportion were ELBW (0.7% according to 1997 data [47]). Survival correlates with birth weight and gestational age, ranging from 11.6% for birth weights <500g to 83.9% for birth weights of 750-1000g to 98.4% for birth weights of 1500-2500g (48).

ELBW children, who are typically born at or before 27 weeks' gestational age, are at greater risk than their higher birth weight counterparts for the various complications of premature birth, including chronic lung disease, severe brain injury, necrotizing enterocolitis, nosocomial infections, and retinopathy of prematurity (ROP). Rates of severe disability, such as mental retardation, cerebral palsy, blindness, and/or deafness, are also high in this population (49). (Notably, although the mortality rate for

ELBW infants has declined, the proportion of those with severe sequelae has not).

Overall, about 20% of ELBW are significantly disabled (50); this proportion rises to 50% among infants born between 500-750g (51).

As they age, ELBW children attain lower growth measurements than their peers (52) and are more likely to develop deficits in executive function (affecting planning, sequencing, and inhibition) and limitations in cognition, sensation, mobility, and self-care (53-55). They experience significantly more neurologic problems than controls, as well as reduced visual-motor function, visual-perceptual abilities, and attention span (56). Extremely low birth weight has been linked to impaired cognitive and motor development in preschool-age children (57) and the need for special education services in school-age children (50). Furthermore, school-age ELBW children as a group score significantly lower than controls on IQ tests, school achievement tests, and motor performance (58). These difficulties follow surviving ELBW children into adolescence, where they continue to have a higher prevalence of visual problems, seizures, developmental delay, learning disabilities, hyperactivity, and use of community resources than controls, although some catch-up growth and improvement in health does tend to occur (59).

Interestingly, although no one has directly investigated the link between ELBW and autism, a strong association has been found between autism and blindness due to retinopathy of prematurity (ROP), a disease for which risk increases as birth weight decreases. In this study (60), undertaken by a group in Sweden, 15 of 27 children in the ROP group (with gestational ages between 25-30 weeks) had autistic disorder, and an additional 4 had autistic-like conditions. The authors speculated that both blindness from

ROP and autism were mediated by brain damage in these children. Only 2 of 14 controls (children with congenital blindness secondary to hereditary retinal disease) were found to be autistic.

Although no cure for autism exists, outcome can be markedly improved by early diagnosis and intervention (61-63). Current intervention strategies recommended by the American Academy of Child and Adolescent Psychiatry and the American Academy of Pediatrics include behavior management, structured play therapy, early developmental education or school-based special education, and speech, occupational, and physical therapy (64, 65). The National Research Council issued a detailed report in 2001 (66) with an analysis of available interventions and recommendations for schools, parents, and the community on educating children with autism. Pharmacologic treatment is also available both for autism-related behaviors and for concurrent psychiatric conditions (67-71). In recent years, encouraged by the development of better treatment options and diagnostic instruments and by growing concerns over the prevalence of autism, health professionals have placed increasing emphasis on the importance of early screening and diagnosis of autism and ASDs (72-73, 64).

In this context, it is vitally important that potential risk factors for autism be defined and investigated. In part one of this study, a sample population of ELBW infants was tested for autistic behaviors using three instruments, the Autism Diagnostic Observation Schedule (ADOS [74]), Autism Behavior Checklist (ABC [75]), and Autism Screening Questionnaire (ASQ [76]). Results of the ADOS, an assessment designed to differentiate among autism proper, ASDs, and nonspectrum diagnoses based on the number and severity of observed behaviors, were used as the primary outcome measure.

In addition, the Vineland Adaptive Behavior Scales (77) were administered to assess level of development in communication, socialization, and daily living skills.

Given that extreme prematurity is known to put children at risk for a host of developmental and behavioral sequelae, and that the incidence of ELBW survivors and prevalence of ASDs have both risen within a similar time frame, we hypothesized that this group of children was more likely than the average population to display autism-related social and communication deficits and behavioral abnormalities. The primary goal of this pilot study was to determine if a more extensive investigation into the link between extreme prematurity and autistic behavior is warranted. Because early diagnosis and treatment are very important in determining future outcome, this study was designed to help clarify whether ELBW is a risk factor for ASDs and whether routine screening for autism is called for in this population of children.

The second part of this study approached the question of low birth weight as a risk factor for ASDs from a retrospective angle. A case-control study was performed using the medical records of children seen in a Developmental Disabilities Clinic. This study compared the birth weights of children with autism or PDD to those of controls with mental retardation (MR) or developmental disabilities outside the autism spectrum. Using results gathered in part one of the study, it was hypothesized that children with autism or PDD would, on average, have lower birth weights than non-autistic controls and would also be more likely to fall into LBW, VLBW, or ELBW categories.

Statement of Purpose

Our primary objective in both parts of this study was to determine whether low birth weight in general, and extremely low birth weight in particular, is linked to the development of autism and pervasive developmental disorders later in childhood. Our secondary objective was to investigate the role of adverse perinatal factors in the etiology of autism spectrum disorders.

In the first part of the study, we hypothesized that a cohort of children born at ELBW (<1,000 grams) would demonstrate a higher prevalence of autistic behaviors and autism-like social and communication deficits than the average population.

In the second part of the study, we hypothesized that children with autism or PDD would have lower mean birth weights than non-autistic controls, and would be more likely to fall into low birth weight, very low birth weight, or extremely low birth weight categories.

Methods

I. ELBW and Development of Autistic Behaviors

Study Population

In part one of this study, we conducted a pilot study with a cohort of ELBW children to determine whether a link between ELBW and the development of autistic behaviors later in childhood might exist. Study participants were drawn from patients of the Newborn Follow-Up (NBFU) Clinic at The Children's Hospital of Alabama. Children between the ages of 3 and 7, with birth weight less than 1,000 grams, were eligible for the study. Only patients who lived within one hour of the clinic were recruited, and children with significant neurologic impairments such as blindness, profound deafness, and cerebral palsy were excluded due to the difficulty of performing the ADOS reliably. Parents of children who met the criteria for the study were contacted by phone (in the majority of cases) or at clinic visits. Given constraints of time and resources, the decision was made not to include a control group in order to maximize the number of ELBW subjects that could be tested, and to reduce investigator bias by having a selection of videotaped ADOS sessions reviewed by a secondary scorer, unaware of the context of the study.

Study Design

Approval was obtained from the Institutional Review Board at the University of Alabama at Birmingham and from the Human Investigations Committee (HIC) at the Yale University School of Medicine. Informed parental consent was obtained at the beginning of each testing session. Three validated assessment tools, the Autism

Diagnostic Observation Schedule, Vineland Adaptive Behavior Scales, and Autism Behavior Checklist, in addition to the experimental Autism Screening Questionnaire, were used to evaluate each child's development, behavior, communicative abilities, and social skills (see Appendix B for a brief overview of these assessments). Scores on the Vineland, ABC, and ASQ were derived from parental responses, and ADOS scores were obtained from observation of the child's behavior during a set of language-appropriate semi-structured activities. The ADOS module to be used was based on the child's verbal level as reported by the parent; module 1 was used for children without spontaneous phrase speech, module 2 for those with flexible phrase speech but not fluency, and module 3 for those with verbal fluency (at the level of a typical 4-year-old child). ADOS sessions were videotaped with parental permission, and were scored by the test administrator.¹ As mentioned above, a small sample of these videotaped sessions was scored independently by an ADOS-certified secondary scorer.

Demographic information, pregnancy and birth history, medical history, and family history were obtained from the parent, as well as a list of medications taken by the child. Discharge summaries and psychological tests from the subject's chart were reviewed to provide additional information about neonatal history and to obtain scores for previously administered IQ tests.

Following the study, a report of the outcomes of the four assessments was generated for each child, and distributed to parents and the NBFU clinic. Follow-up treatment and repeated assessments through the NBFU and Sparks clinics were provided for children with unusual or worrisome test results.

¹ The ADOS administrator, the writer of this paper, underwent a one-week ADOS training session and established reliability with an ADOS-certified colleague prior to administering the test for research purposes.

Outcomes

The results of the ADOS tests were used as the primary outcome measure, with results of the Vineland, ABC, and ASQ contributing to the overall analysis. ADOS results were compared to published data on the prevalence of autism spectrum disorders in the general population; Vineland results were compared to established norms. Within the ELBW group, performance on these tests was analyzed with reference to individual birth weight and gestational age to determine if correlations existed between these factors and the demonstration of autistic behaviors. Because of concerns that low IQ might contribute to false positive results on the ADOS, we controlled for IQ (as measured by the Bayley Scales of Infant Development, corrected for gestational age, and the Differential Ability Scales [DAS]) in these correlations. A variety of participant characteristics and perinatal factors (e.g., mental retardation, seizure disorder, retinopathy of prematurity, intraventricular hemorrhage, bronchopulmonary dysplasia) were also reviewed with reference to performance on the ADOS.

Statistical Analysis

Given the nature of the study, and the relatively small number of children eligible for recruitment, we designed the protocol to include as many ELBW children as possible during the active phase of the trial. In addition to recording the absolute number of “positive” scores on the ADOS and its subsections, we estimated prevalence within a 95% confidence interval. Within the ELBW group, the Kendall rank correlation coefficient was used to analyze correlations between continuous variables such as birth weight and test scores, with a partial correlation coefficient used to control for the effects

of IQ. Among the ADOS classification groups (autism range, ASD range, and normal range), the Fisher exact probability test was used to compare categorical variables and the Kruskal-Wallis test was used to compare birth weights. A conventional 2-sided p value of less than 0.05 was retained throughout.

Role of Student

The medical student and writer of this thesis, under the supervision of Dr. Myriam Peralta and Dr. Crayton Fargason (Department of Pediatrics, University of Alabama at Birmingham) and Dr. Fred Volkmar (Child Study Center, Yale University School of Medicine), helped to design the study and obtain Institutional Review Board approval. The student and an assistant recruited all ELBW clinic patients for the study. The student was trained in ADOS administration and administered and scored all ADOS tests, which were videotaped for secondary review by Kirsten Bailey, a psychology fellow at the University of Alabama at Birmingham. The student also obtained all demographic information from the parents and patient charts and administered all ABC and ASQ parent questionnaires. Approximately 2/3 of the Vineland tests were conducted by the student, with the remaining 1/3 conducted by another person involved with the study. In addition, under the direction of the advisors named above, the student performed the statistical analysis for both portions of this study.

II. Retrospective Analysis of Birth Weight in Autism and ASDs

Study Participants

In the second part of the study, cases and controls were drawn from patients seen

in the Developmental Disabilities Clinic of the Child Study Center at Yale University School of Medicine. All patients seen in the clinic for whom data on birth weight and IQ were available were included in the study.

Study Design

After Yale HIC approval was obtained, a review of medical records of children with and without autism spectrum disorders was performed. The purpose of this case-control study was to compare birth weights of children with autism and other ASDs to those of non-autistic controls. Participants were divided into cases, which were then split into two groups according to a diagnosis of autism or PDD, and controls. Autism or PDD had been diagnosed by experts at the Developmental Disabilities Clinic.² Control subjects had been diagnosed with a variety of non-autistic disorders including attention deficit disorder, bipolar disorder, blindness, cerebral palsy, conduct disorder, depression, language disorder, learning disability, nonverbal learning disability, reactive attachment disorder, social anxiety disorder, schizophrenia, Tourette's syndrome, or simple mental retardation. Due to diagnostic criteria that overlap with disorders within the autism spectrum, patients with Childhood Disintegrative Disorder or Multiplex Developmental Disorder were excluded to avoid confounding the data.

² Interrater reliability of clinical diagnosis of autism and PDD based on DSM-IV criteria has been shown to be excellent among experienced clinicians. In particular, the group of practitioners at the Yale Child Study Center, who diagnosed the children in this study, participated in and published results from the DSM-IV autism field trial. See Klin A, Lang J, Cicchetti DV, Volkmar FR. 2000. Brief report: interrater reliability of clinical diagnosis and DSM-IV criteria for autistic disorder: results of the DSM-IV autism field trial. *J Aut Dev Disord.* 30(2):163-7.

Outcomes

The primary outcome measures were birth weight and gestational age. For further analysis, cases and controls were divided according to presence or absence of mental retardation, defined as full-scale intelligence quotient (FSIQ) < 70 on the Kaufman Assessment Battery for Children (KABC), Leiter International Performance Scale, Wechsler Intelligence Scale for Children (WISC), or Wechsler Adult Intelligence Scale (WAIS). Secondary outcomes included a variety of factors contributing to perinatal adversity, as reported by the child's parent. These factors include general concern about the baby's condition, excessive maternal bleeding, meconium staining, maternal fever and/or infection, forceps use, nuchal cord, placental abnormalities, jaundice, use of incubator, feeding difficulties, or oxygen supplementation.

Statistical Analysis

The number of subjects in each group needed to demonstrate a statistically significant difference among the groups was calculated beforehand, considering both alpha and beta error. Using available birth statistics, we assumed a standard deviation in birth weight of 500g. We predicted that 63 subjects per group would be needed to detect a difference of 250g with a two-sided α value of 0.05. Continuous variables were compared using one-way analysis of variance; the chi-square test was used for categorical variables. Statistical significance was determined by two-sided p value of .05.

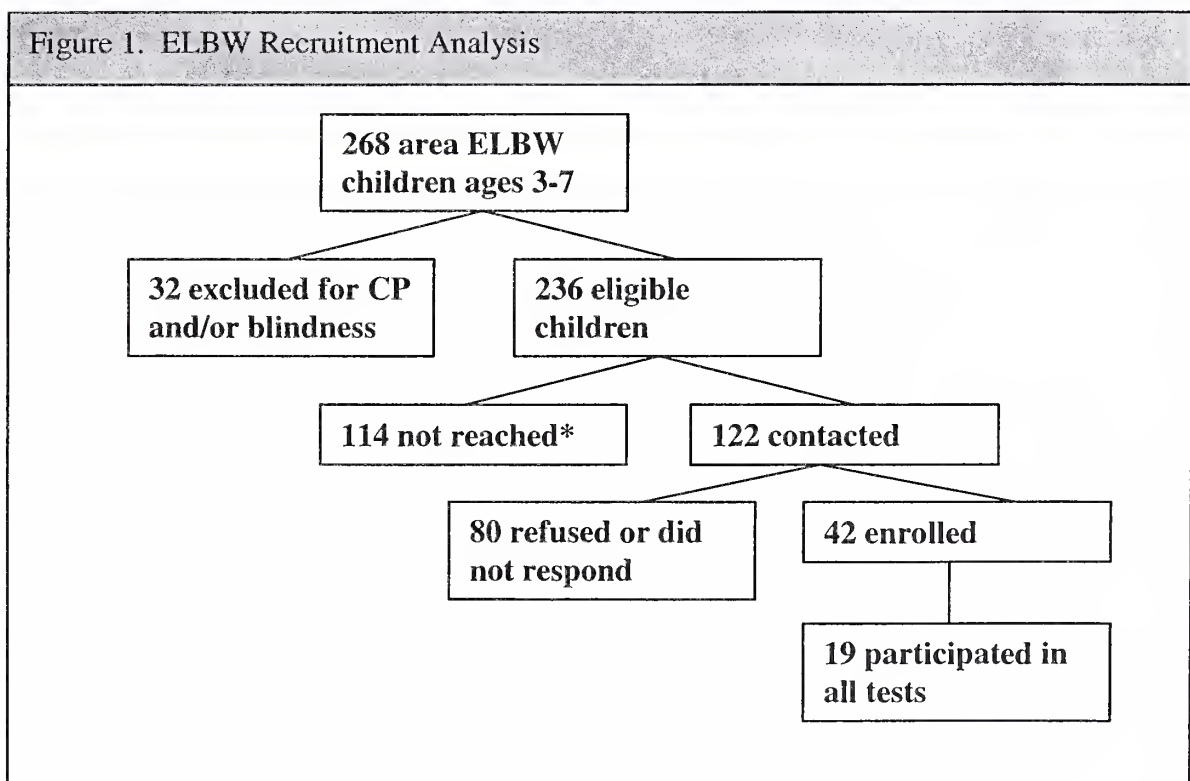
Role of Student

In this portion of the study, the medical student obtained, organized, and analyzed data from an existing database of patients seen in the Developmental Disabilities Clinic, under the direction of Dr. Fred Volkmar.

Results

I. Autism/ELBW trial

Of the 268 ELBW children who met criteria for the study, 27 were excluded for cerebral palsy, 2 for blindness, and 3 for both cerebral palsy and blindness, leaving 236 eligible subjects. None of these children had hearing loss severe enough to merit exclusion. Of the 236 eligible subjects, 122 were contacted, 42 were enrolled in the study, 8 refused, and 72 did not return messages regarding the study. 114 children could not be contacted due to wrong numbers or no answer. Reasons given for refusal included distance from clinic (1), serious illness (1), time constraints (2), and lack of interest (4). Of the 42 subjects initially enrolled in the study, 19 completed all tests required for the study and were included in the analysis. (Figure 1)



ELBW, extremely low birth weight; CP, cerebral palsy

* due to unavailability of current contact information or failure to answer telephone

The baseline characteristics of the 19 children included in the analysis are detailed in Table A. Many of the study participants, who were born at weights ranging from 520 to 1000 grams, had been affected by various sequelae of prematurity, including retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), and cognitive deficits. Using IQ <70 on most recent test (Bayley corrected mental age or DAS general conceptual ability) as the criterion for mental retardation, four participants were determined to have MR.

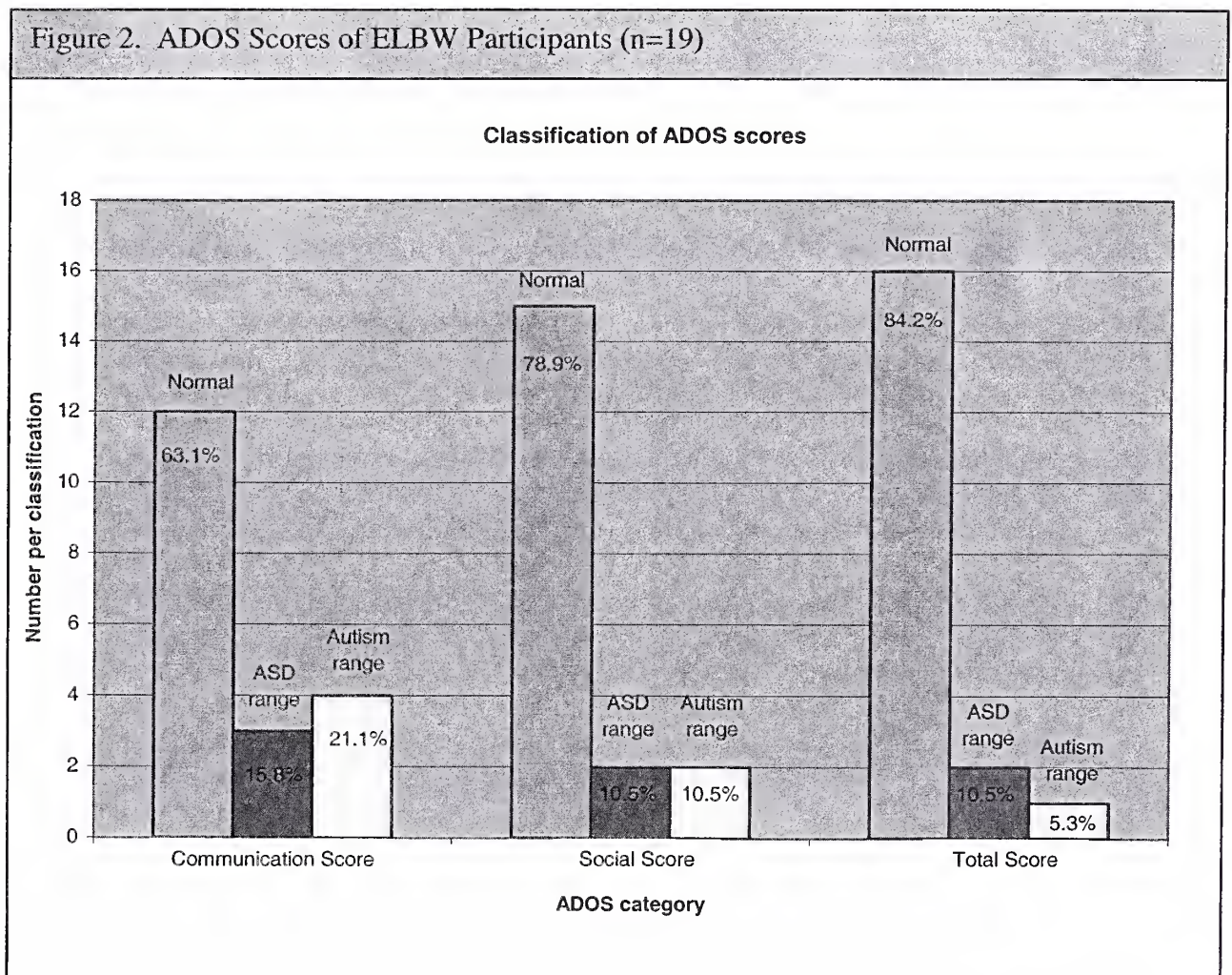
Table A. ELBW Study Participant Characteristics	
N	19
Mean age	5.33 years (SD 0.95, range 3.25-6.7)
Mean birth weight	853.47 grams (SD 142.38, range 520-1000)
Mean gestational age	26.74 weeks (SD 1.88, range 23-30)
Sex	9 female (47.4%) 10 male (52.6%)
Race	9 white (47.4%) 10 black (52.6%)
ROP	9 (47.4%)
Stage 1	5 (26.3%)
Stage 2	3 (15.8%)
Stage 3	1 (5.3%)
IVH	6 (31.6%)
Grade 1	3 (15.8%)
Grade 2	2 (10.5%)
Grade 3	1 (5.3%)
BPD	4 (21.1%)
IQ < 70*	4 (21.1%)

ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia

* using latest result on Bayley Scales of Infant Development, corrected for gestational age, or the Differential Ability Scales

Out of 19 participants, 2 (10.5%) had an ADOS total score in ASD range and 1 other (5.3%) had a score in the autism range. Several children scored abnormally on one or more of the ADOS subsets. For ADOS communication scores, 3 (15.8%) fell in ASD range and 4 (21.1%) in autism range; for social scores, 2 (10.5%) fell in ASD range and 2 (10.5%) in autism range. (Figure 2)

Figure 2. ADOS Scores of ELBW Participants (n=19)



ADOS, Autism Diagnostic Observation Schedule; ELBW, extremely low birth weight; ASD, autism spectrum disorder

Overall, 3 out of the 19 study participants, or 15.8% (standard error 16.4%; 95% confidence interval, -0.6-32.2%), had ADOS total scores in the ASD (2) or autism (1) range. All three were males between the ages of four and six at the time of testing; two were white and one was black. Only one study participant scored within the ASD range on both the ADOS and the parental questionnaires, the ASQ and ABC. No other participants scored abnormally on the questionnaires. Test results for children with abnormal ADOS scores are summarized in Table B.

Table B. Test Results for Children with Abnormal ADOS Scores					
	ADOS social	ADOS comm.	ADOS total	ABC	ASQ
1		+			
2	+	++	+	++	+
3		+			
4		++			
5	+				
6		+			
7		++			
8	++		+		
9	++	++	++		

ADOS, Autism Diagnostic Observation Schedule; ABC, Autism Behavior Checklist; ASQ, Autism Screening Questionnaire

Participants with abnormal total ADOS scores (suggestive of autism or ASD) are highlighted.

+ within testing range for an ASD

++ within testing range for autism

ADOS sessions for 6 of the 19 participants, including 2 of the 3 with abnormal total scores, were reviewed on videotape and rescored by an independent ADOS-certified scorer, blinded to the initial results. The two children with abnormal initial scores were again found to be within the autism or ASD range by this secondary reviewer. The

remaining four subjects were assigned secondary scores that were the same or slightly higher than their initial ADOS scores.

Mean Vineland standard scores for ELBW children were more than one standard deviation below the national norm in all categories (Table C), although within the ELBW group there were no significant correlations between birth weight and standard or composite scores ($\tau = 0.054$, $p = 0.752$ communication domain; $\tau = 0.251$, $p = 0.140$ socialization domain; $\tau = 0.222$, $p = 0.193$ composite score). Domain scores were uniformly low; mean socialization and communication scores were not significantly different from daily living skills or from composite score ($p = 0.363$). The participant with ASD-level scores on the ADOS, ABC, and ASQ had a relatively low socialization raw score of 60 compared to scores of 74 in the communication and 88 in the daily living skills domains. The other two participants with abnormal ADOS total scores did not have socialization scores that were appreciably lower than those in the other domains (their scores for the socialization, communication, and daily living skills domains were, respectively, 70, 80, 67 and 57, 54, 32).

Table C. ELBW Vineland Standard Scores Compared to National Norms		
	ELBW	NORM
Communication	83.42 (13.125)	100 (15.00)
Daily Living Skills	82.84 (13.129)	100 (15.00)
Social	84.68 (14.708)	100 (15.00)
Composite	77.37 (13.238)	100 (15.00)

ELBW, extremely low birth weight.

Because the scoring system and diagnostic cut-offs vary among the three ADOS modules used in this study, we used the module with the most data points (module 3, $n=14$) to assess correlation between ADOS scores and other factors; correlations not including the ADOS used data from all participants ($n=19$). *Within* the ELBW group, birth weight did not correlate significantly with scores on ADOS communication domain ($\tau = 0.061$, $p=0.775$), social ($\tau = 0.366$, $p=0.082$) domain, or total ($\tau = 0.297$, $p=0.15$). There was no difference in birth weight among the three categorical ADOS classifications (normal, ASD-range, or autism-range total score; $p=0.32$).

Likewise, there was no correlation found between birth weight and total scores on the ABC ($\tau = 0.047$, $p=0.779$) or ASQ ($\tau = 0.248$, $p=0.156$). However, gestational age was found to correlate positively with ADOS social ($\tau = 0.650$, $p=0.004$) and total scores ($\tau = 0.525$, $p=0.019$); that is, later gestational age was related to more abnormal scores. IQ was controlled for in the analysis of ADOS, ABC, and ASQ scores.

Scores on the Bayley Scales of Infant Development, corrected for gestational age, correlated positively with ADOS social scores ($\tau = 0.468$, $p=0.037$), although no association was seen between DAS General Conceptual Ability and ADOS results ($\tau = 0.082$ - 0.128 , $p=0.568$ - 0.708).

When the perinatal and childhood histories of the participants who reached abnormal cutoffs in the social ($n=4$) or communication ($n=7$) ADOS domains, or on the ADOS total ($n=3$), were compared with the rest, there were no significant differences observed in the occurrence of ROP, IVH, BPD, cardiac anomalies, seizure disorders, developmental brain abnormalities, or mental retardation, or in the mode of delivery

($p=0.17-1.00$; see Table D). None of the study participants had a history of congenital infection, traumatic brain injury or other postnatal injury, inborn error of metabolism, maternal drug use, forceps use, or neonatal resuscitation.

Table D. Characteristics of Children with Normal vs. Abnormal ADOS Scores

Factor	Communication Score			Social Score			Total Score		
	Normal n=12	Abn n=7	p value	Normal n=15	Abn n=4	p value	Normal n=16	Abn n=3	p value
ROP	7 (58%)	2 (29%)	0.350	8 (53%)	1 (25%)	0.582	8 (50%)	1 (33%)	1.000
IVH	5 (42%)	1 (14%)	0.333	5 (33%)	1 (25%)	1.000	6 (38%)	0	0.517
BPD	4 (33%)	0	0.245	4 (27%)	0	0.530	4 (25%)	0	1.000
Cardiac Anomaly	6 (50%)	1 (14%)	0.173	6 (40%)	1 (25%)	1.000	6 (38%)	1 (33%)	1.000
Seizure Disorder	1 (8%)	1 (14%)	1.000	2 (13%)	0	1.000	2 (13%)	0	1.000
Developmental Brain Abnormality	1 (8%)	1 (14%)	1.000	2 (13%)	0	1.000	2 (13%)	0	1.000
Mental Retardation	3 (25%)	1 (14%)	1.000	2 (13%)	2 (50%)	0.178	3 (19%)	1 (33%)	1.000
Cesarean Section	7 (58%)	4 (57%)	1.000	9 (60%)	2 (50%)	1.000	9 (56%)	2 (66%)	1.000

ADOS, Autism Diagnostic Observation Schedule; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; Abn, abnormal.
p values determined by Fisher's Exact Test (2-sided).

II. Case-control study

Out of 300 children for whom all necessary data were available, 4 were excluded for diagnoses that did not fall squarely into either PDD or control groups: Childhood Disintegrative Disorder (2) and Multiplex Developmental Disorder (2). We included the remaining 296 subjects in the analysis, including 74 patients with autism, 132 patients with PDD, and 90 non-autistic controls.

As demonstrated in Table E, there were no significant differences among the groups in age (mean 12.85-14.69 years, $p=0.055$) or gender distribution ($p=0.944$). The

proportion of subjects with mental retardation (IQ<70) was 45% in the autism group, compared to 12% in the PDD group and 21% in the control group ($p<0.0005$).

Table E. Baseline Patient Characteristics of Cases and Controls				
	Autism	PDD	Control	p value
N	74	132	90	
Mean (SD)	14.69 (6.48) years	12.85 (4.35) years	13.6 (5.31) years	0.055
age				
Sex	14F (19%) 60M (81%)	24F (18%) 108M (82%)	18F (20%) 72M (80%)	0.944
IQ				<0.0005*
<70	33 (45%)	16 (12%)	19 (21%)	
≥70	41 (55%)	116 (88%)	71 (79%)	

PDD, pervasive developmental disorder.

* statistically significant (95% confidence interval)

Table F shows the results of the analysis. Mean birth weight (\pm SD) was 3458.4 \pm 695.0 grams for the autism group, 3444.8 \pm 483.4 grams for the PDD group, and 3364.3 \pm 664.6 grams for the control group ($p=0.523$). When birth weights for children with IQ<70 were compared, there was a noticeable but nonsignificant trend toward higher birth weight in the autism group (Figure 3; $p=0.132$); mean birth weight for those with low IQ was 3514.6 \pm 705.7 for the autism group, 3316.8 \pm 449.7 for the PDD group, and 3138.5 \pm 614.0 for the controls. Birth weights were similar across the three groups for children with IQ \geq 70 ($p=0.858$), for female subjects ($p=0.840$), and for male subjects ($p=0.554$).

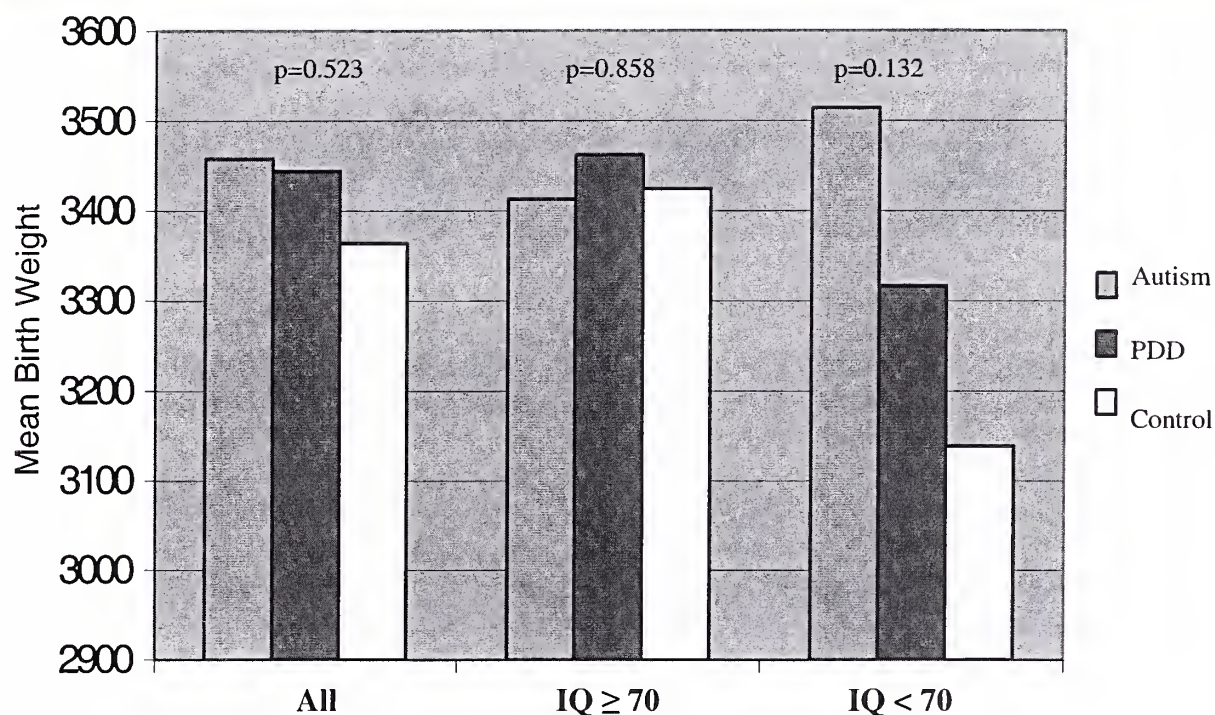
Table F. Birth Weight and Gestational Age in Cases and Controls

	Autism	PDD	Control	p value
N	74	132	90	
Mean (SD) birth weight, in grams	3458.42 (695.0)	3444.82 (483.4)	3364.27 (664.61)	0.523
	IQ<70 3514.55 (705.7)	IQ<70 3316.76 (449.7)	IQ<70 3138.46 (614.0)	0.132
	IQ≥70 3413.25 (691.7)	IQ≥70 3462.48 (487.0)	IQ≥70 3424.70 (653.0)	0.858
	F 3425.32 (521.6)	F 3341.6 (456.8)	F 3336.49 (451.6)	0.840
	M 3466.15 (733.1)	M 3467.75 (488.14)	M 3371.21 (710.4)	0.554
Mean (SD) gestational age, in weeks	39.42 (2.04)	39.37 (1.90)	39.20 (2.69)	0.825
Birth weight category				
NBW (≥2500g)	70 (94.6%)	127 (96.2%)	84 (93.3%)	
LBW (<2500g)	2 (2.7%)	5 (3.8%)	5 (5.6%)	
VLBW (<1500g)	2 (2.7%)	0	0	
ELBW (<1000g)	0	0	1 (1.1%)	
Total <2500g	4 (5.4%)	5 (3.8%)	6 (6.7%)	0.623

NBW, normal birth weight; LBW, low birth weight; VLBW, very low birth weight; ELBW, extremely low birth weight; PDD, pervasive developmental disorder.

Mean gestational age was 39.4 ± 2.0 weeks for the autism group, 39.4 ± 1.9 weeks for the PDD group, and 39.2 ± 2.7 weeks for the controls ($p=0.825$). Only 4 (5.4%) of the autism group, 5 (3.8%) of the PDD group, and 6 (6.7%) of the control group fell into one of the low birth weight categories (LBW, VLBW, or ELBW); there was no significant difference in the percentage of children with birth weight < 2500 grams among cases and controls ($p=0.623$).

Figure 3. Comparison of Mean Birth Weight Among Cases and Controls



When adverse perinatal events and conditions (parentally reported) were analyzed, there were no differences observed among groups in overall concern about the baby's condition during labor ($p=0.992$), excessive bleeding before ($p=0.365$) or during ($p=0.563$) labor, meconium staining ($p=0.066$), maternal fever and/or infection ($p=0.543$), forceps use ($p=0.652$), nuchal cord ($p=0.201$), or placental abnormalities (previa or abruptio; $p=0.789$). Likewise, there were no differences in treated ($p=0.322$) or untreated ($p=0.929$) jaundice, use of incubator ($p=0.251$), feeding difficulties ($p=0.635$), or oxygen supplementation ($p=0.661$). See Table G for a summary of these

results. There were also no differences in the proportion of cases in each group with 0-1, 2-3, or >3 adverse conditions ($p=0.849$). The number of data points varies with each of these factors ($n = 190-289$), as full perinatal data was not available for all subjects.

Table G. Summary of Parentally Reported Adverse Perinatal Factors in Cases and Controls

Factor	Total n	Adverse factor reported			p value
		Autism group	PDD group	Control group	
Concern over fetal condition in labor	246	15/59 (25.4%)	28/110 (25.5%)	19/77 (24.7%)	0.992
Excessive bleeding before delivery	288	3/73 (4.1%)	2/127 (1.6%)	1/88 (1.1%)	0.365
Meconium	249	3/59 (5.1%)	15/111 (13.5%)	4/79 (5.1%)	0.066
Maternal fever/infection	190	3/46 (6.5%)	9/82 (11.0%)	4/62 (6.5%)	0.543
Excessive bleeding during delivery	249	1/59 (1.7%)	5/111 (4.5%)	2/79 (2.5%)	0.563
Forceps use	251	5/59 (8.5%)	11/111 (9.9%)	5/81 (6.2%)	0.652
Nuchal cord	289	5/73 (6.8%)	14/127 (11.0%)	4/89 (4.5%)	0.201
Placenta previa or abruptio	285	3/72 (4.2%)	3/124 (2.4%)	3/89 (3.4%)	0.789
Untreated transient jaundice	280	10/67 (14.9%)	21/125 (16.8%)	15/88 (17.0%)	0.929
Jaundice requiring phototherapy	250	13/58 (22.4%)	15/112 (13.4%)	14/80 (17.5%)	0.322
Incubator use	287	6/70 (8.6%)	12/128 (9.4%)	14/89 (15.7%)	0.251
Feeding difficulties	246	7/56 (12.5%)	20/111 (18.0%)	14/79 (17.7%)	0.635
Oxygen supplementation	285	5/70 (7.1%)	13/127 (10.2%)	10/88 (11.4%)	0.661

PDD, pervasive developmental disorder.

Discussion

Taken together, our pilot study exploring the possible connection between extremely low birth weight and the later development of autistic behaviors, and our case-control analysis of birth weight and gestational age in autistic, PDD, and control populations, raise several interesting points about the nature and etiology of autism. The first study suggests that ELBW children may be at risk for developing autism-like deficits in communication and reciprocal social interaction. The second leads us to conclude that low birth weight is not a major risk factor for autism and PDD in a larger group of children.

In our study of 19 ELBW children, a higher-than-expected number scored in the autism and ASD ranges on the ADOS tests, suggesting that these children may be at higher risk than children of normal birth weight for developing deficits in communication and social interaction suggestive of an ASD. It should be emphasized that scoring abnormally on a subset of the ADOS does not, in itself, indicate a diagnosis of ASD; rather, it is the total score that counts. Indeed, the fact that only one child scored in the ASD range on all administered tests (and therefore likely falls into the diagnostic category of PDD-NOS) indicates that most of the children did not meet the criteria for an ASD despite their abnormal performance on the ADOS. Overall, 3/19 (15.8%) children had an ASD- or autism-level total score on the ADOS, and 1/19 (5.3%) had ASD-level scores on all tests; by comparison, estimated prevalence for ASDs in the general population is approximately 60/10,000 (0.6%).

Although ELBW children scored abnormally on the ADOS with surprising frequency, we saw no correlation *within* the group between birth weight and ADOS

scores, nor between birth weight and ABC, ASQ, or Vineland scores. This lack of correlation may be due to the small sample size or to the possibility that while being born at ELBW increases risk, there are no significant differences in risk within the small 500 gram weight range. We did, however, see a positive correlation between gestational age and ADOS social scores. This correlation leads us to wonder whether some sort of growth restriction, resulting in children who have relatively late gestational ages but low birth weights, might play into later impairments in social interaction, although with such a small sample size this finding is difficult to generalize. Higher IQ measured earlier in life (as demonstrated by the Bayley Scales of Infant Development) correlated with higher ADOS social scores, but there was no association between social scores and IQ measured later in life (measured by the DAS). These findings help to dismiss notions that *low* IQ might contribute to false positive results on the ADOS. Overall, correlations using ADOS scores are necessarily imperfect and should be interpreted with caution because the ADOS uses *cutoff* scores for diagnosis of PDD or of autism. According to the ADOS design, whether a score falls above or below a given cutoff (which is a different number for each of the modules) is more significant than the absolute score. To correct partially for this, we used only module 3 data (the module given to the majority of the participants) for correlations.

Mean Vineland standard scores for the ELBW children were more than one standard deviation below the norm in all domains, a finding that was not particularly surprising given the significant developmental delays and limitations in cognitive and executive function often seen with in this group of children. Patterns of Vineland domain scores for developmentally disordered children have been previously described, and can

be useful in discriminating autism from other disorders. One group (78) has shown that autistic children tend to have low socialization scores for chronological and mental age (a ratio of actual to age-predicted socialization scores 3.5 standard deviations below the normative sample is most indicative of autism). This method, however, did not prove useful in distinguishing PDD from other diagnoses. Other studies (79-81) have identified patterns of low socialization performance, intermediate communication skills, and relatively high function in terms of daily living skills for the autistic population. We did not observe such patterns in the ELBW group as a whole (in which performance in all adaptive behavior domains was uniformly low), but did note a pattern suggestive of autism in the raw domain scores of the one participant who scored in the ASD domain on all administered tests. This finding increases our suspicion that this individual's diagnosis of an ASD was correct.

This pilot study has several limitations. Unfortunately, despite efforts to recruit enough subjects for statistical significance, only 19 subjects could be fully tested, thus limiting the power of the study. Therefore, our data are insufficient to estimate the prevalence of ASDs in the ELBW population as a whole. We cannot exclude the possibility that our results occurred by chance alone, or as a result of patient self-selection (i.e., the possibility that parents with "problem" children were more eager to participate in the study). However, our results – strengthened by the corroboration of a blinded secondary ADOS scorer – do point to a potential connection between ELBW and autistic behaviors that should be further investigated on a larger scale.

Another potential weakness centers around the lack of controls and the resulting potential for investigator bias. Early in the design of this pilot study, the decision was

made not to include a control group of normal birth weight children in order to maximize testing of ELBW children in the limited time available. Because standardized norms exist for each of the assessment tools used, the ELBW children in the study were compared against these norms rather than against a control group. Concerns about investigator bias in the ADOS test were addressed by having a second person, unaware of the context of the study, rescore a random sample of ADOS tests. The other three instruments used – the Vineland, ABC, and ASQ – were based either exclusively or primarily on parental response and were thus less subject to investigator bias.

Conversely, the exclusion of children with cerebral palsy (due to the difficulty of administering the ADOS to such children) may have contributed to a falsely low number of abnormal scores. Cerebral palsy is associated with neurobehavioral disorders, including autism, in up to 50% of cases (82). Although there were no children with hearing loss severe enough to merit exclusion on our particular study, it should also be noted for future investigations that an association between autism and deafness has been shown to exist. One group (83) found moderate-severe to profound hearing loss in 10-15% of autistic cases.

The ADOS is designed to catch abnormalities in communication and social interaction that are relatively specific to disorders in the autism spectrum. Our findings suggest that the subtle deficits picked up during ADOS testing in several of the ELBW children are *similar* in character to those seen in autism and autism spectrum disorders, even though these children would not be diagnosed as having an ASD. Furthermore, given that outcomes in autistic children can be markedly improved by early intervention, it is possible that timely recognition and management of these subtle problems with

communication and sociability may be beneficial to those ELBW children who are affected.

Thus, although our data cannot be used reliably to estimate the prevalence of ASD in the ELBW population, we offer clinically interesting results that we hope will inform the design of larger, controlled studies. The sample size needed for a definitive study comparing ASDs in ELBW and control populations would require between 200 and several thousand subjects per group, depending on initial assumptions, and would likely necessitate a coordinated effort by several institutions caring for ELBW children.

For the second part of this work – the case-control study – we calculated sample size ahead of time to avoid the difficulties with low statistical power encountered in the first part. Our case and control groups were similar in mean age and gender distribution. As expected, the autistic group had a higher incidence of mental retardation than the other two groups. We observed no significant differences in birth weight or gestational age among the autism, PDD, and control groups as a whole or when the groups were stratified according to IQ or gender. In the active debate over birth-related etiologies of autism, this finding supports those studies that suggest that birth weight is *not* a significant risk factor for autism. Likewise, we found no relationship between adverse perinatal factors (nonreassuring fetal status during labor, excessive maternal bleeding, meconium staining, maternal fever or infection, forceps use, nuchal cord, placental abnormalities, hyperbilirubinemia, incubator use, feeding difficulties, or oxygen supplementation) and the development of autism or PDD.

Interestingly, within the subgroup of participants with mental retardation, autistic subjects had *higher* birth weights than PDD subjects, who in turn had higher birth

weights than controls, although this trend was not significant within the 95% confidence interval. Low birth weight has been classically associated with cognitive deficits – secondary to neurologic damage (from trauma, asphyxia, or spontaneous intracerebral hemorrhage) related to the underdeveloped brain and body of the premature infant – but the autistic children with MR had even higher birth weights than the autistic group as a whole. This implies that cognitive deficits in autistic children may stem from a secondary process unrelated to birth parameters, perhaps the same neurologic process that has caused the autism itself. Such an idea fits nicely with the abnormal brain growth hypothesis of autism, referenced earlier in this paper (17), in suggesting that something happens to the brain *after* birth (be it formation of abnormal neural connections, glial proliferation, or some other as yet undefined process) to cause autism and also, in many cases, concurrent mental retardation.

In conclusion, the findings of these two related studies produce an interesting picture about the nature and root causes of autism. Many experts now believe that disorders within the autism spectrum are likely the end result of a *variety* of factors, genetic and/or environmental, rather than the consequence of a single defined set of events or insults. That is, the cause of autism is almost certainly not the same for all affected individuals. Thus, while our data demonstrate that low birth weight is unlikely to be a major risk factor for ASDs, it is possible that the small subgroup born at ELBW (and thus at special risk for neurologic sequelae) may have a tendency to develop autism-like behavioral derangements even if low-birth-weight children in general do not. Given the striking prevalence of subtle deficits in social and communication skills seen in the ELBW children in this study, as well as the potential for correcting these deficits with

early intervention, we eagerly await the generation of additional data to determine whether screening ELBW children for autism-like deficits is warranted.

References

1. Interagency Autism Coordinating Committee. Ten-Year Framework for Autism. Presented at Autism Summit Conference. Washington, DC: 2003.
2. American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association. 886 pp.
3. Gillberg C. 1990. Autism and pervasive developmental disorders. *J Child Psychol Psychiatr*. 31(1):99-119.
4. Fombonne E. 1998. Epidemiological surveys of autism. In *Autism and Pervasive Developmental Disorders*. Volkmar F, editor. Cambridge: Cambridge U P. 32-63.
5. Gillberg C, Wing L. 1999. Autism: not an extremely rare disorder. *Acta Psychiatr Scand*. 99(6):399-406.
6. Fombonne E. 1999. The epidemiology of autism: a review. *Psychol Med*. 29(4):769-86.
7. Chakrabarti S, Fombonne E. 2001. Pervasive developmental disorders in preschool children. *JAMA*. 285(24):3093-99.
8. Centers for Disease Control and Prevention. 2000. *Prevalence of autism in Brick Township, New Jersey, 1998*. Atlanta, Ga: Centers for Disease Control and Prevention. Community Report.
9. Baird G, Charman T, Baron-Cohen S, Cox A, Swettenham J, et al. 2000. A screening instrument for autism at 18 months of age: a 6-year follow-up study. *J Am Acad Child Adolesc Psychiatry*. 39(6):694-702.
10. Honda H, Shimizu Y, Misumi K, Niimi M, Ohashi Y. 1996. Cumulative incidence and prevalence of childhood autism in children in Japan. *Br J Psychiatry*. 169(2):228-235.
11. Gurney JG, Fritz MS, Ness KK, Sievers P, Newschaffer CJ, et al. 2003. Analysis of prevalence trends of autism spectrum disorder in Minnesota. *Arch Pediatr Adolesc Med*. 157:622-627.
12. Volkmar FR, Pauls D. 2003. Autism. *Lancet*. 362:1133-41.
13. Trottier G, Srivastava L, Walker CD. 1999. Etiology of infantile autism: a review of recent advances in genetic and neurobiological research. *J Psychiatry Neurosci*. 24(2):103-15.

14. Gillberg C, Coleman M. 1996. Autism and medical disorders: a review of the literature. *Dev Med Child Neurol.* 38(3):191-202.
15. Lauritsen M, Ewald H. 2001. The genetics of autism. *Acta Psychiatr Scand.* 103(6):411-27.
16. Cook EH. 2001. Genetics of autism. *Child Adolesc Psychiatr Clin N Am* 10(2):333-50.
17. Spiker D, Lotspeich L, Kraemer HC, Hallmayer J, McMahon W, et al. 1994. Genetics of autism: characteristics of affected and unaffected children from 37 multiplex families. *Am J Med Genet.* 54(1):27-35.
18. Folstein S, Rutter M. 1977. Infantile autism: a genetic study of 21 twin pairs. *J Child Psychol Psychiatry.* 18:291-321.
19. Folstein SE, Piven J. 1991. Etiology of autism: genetic influences. *Pediatrics.* 87:767-73.
20. Steffenburg S, Gillberg C, Hellgren L, Andersson L, Gillberg IC, et al. 1989. A twin study of autism in Denmark, Finland, Iceland, Norway and Sweden. *J Child Psychol Psychiatry.* 30(3):405-16.
21. Ritvo ER, Jorde LB, Mason-Brothers A, Freeman BJ, Pingree C, et al. 1989. The UCLA-University of Utah epidemiologic survey of autism: recurrence risk estimates and genetic counseling. *Am J Psychiatry.* 146(8):1032-36.
22. Baird TD, August GJ. 1985. Familial heterogeneity in infantile autism. *J Autism Dev Disord.* 15:315-321.
23. Smalley SL. 1998. Autism and tuberous sclerosis. *J Aut Dev Disord.* 28:407-14.
24. Williams PG, Hersh JH. 1998. Brief report: the association of neurofibromatosis type 1 and autism. *J Aut Dev Disord.* 28:567-71.
25. Feinstein C, Ross AL. 1998. Autism: the point of view from fragile X studies. *J Aut Dev Disord.* 28:393-405.
26. Tuchman R, Rapin I. 2002. Epilepsy in autism. *Lancet.* 1(6):352-8.
27. Rosman, NP. 1995. Autism. In *Behavioral and Developmental Pediatrics*. Parker S, Zuckerman B, eds. Boston: Little, Brown & Company. 73-77.

28. Madsen KM, Hviid A, Vestergaard M, Schendel D, Wohlfahrt J, et al. 2002. A population-based study of measles, mumps, and rubella vaccination and autism. *N Engl J Med.* 347(19):1477-82.
29. Wilson K, Mills E, Ross C, McGowan J, Jadad A. 2003. Association of autistic spectrum disorder and the measles, mumps, and rubella vaccine: a systematic review of current epidemiological evidence. *Arch Pediatr Adolesc Med.* 157:628-634.
30. Rutter M, Bailey A, Bolton P, Le Couteur A. 1994. Autism and known medical conditions: myth and substance. *J Child Psychol Psychiatry.* 35(2):311-322.
31. Gillberg C, Billstedt E. 2000. Autism and Asperger syndrome: coexistence with other clinical disorders. *Acta Psychiatr Scand.* 102(5):321-30.
32. Courchesne E, Carper R, Akshoomoff N. 2003. Evidence of brain overgrowth in the first year of life in autism. *JAMA.* 290(3):337-344.
33. Baron-Cohen S, Ring HA, Wheelwright S, Bullmore ET, Brammer MJ, et al. 1999. Social intelligence in the normal and autistic brain: an fMRI study. *Eur J Neurosci.* 11(6):1891-8.
34. Bauman M, Kemper T. 1997. Neuroanatomic observations of the brain in autism. In *The Neurobiology of Autism*. Bauman M, Kemper T, editors. Baltimore: Johns Hopkins UP. 119-145.
35. Deykin EY, MacMahon B. 1980. Pregnancy, delivery, and neonatal complications among autistic children. *Am J Dis Child.* 134(9):860-4.
36. Lord C, Mulloy C, Wendelboe M, Schopler E. 1991. Pre- and perinatal factors in high-functioning females and males with autism. *J Aut Dev Disord.* 21(2):197-209.
37. Bryson SE, Smith IM, Eastwood D. 1988. Obstetrical suboptimality in autistic children. *J Am Acad Child Adolesc Psychiatry.* 27:418-422.
38. Gillberg C, Gillberg IC. 1983. Infantile autism: a total population study of reduced optimality in the pre-, peri-, and neonatal period. *J Aut Dev Disord.* 13(2):153-166.
39. Burd L, Severud R, Kerbeshian J, Klug MG. 1999. Prenatal and perinatal risk factors for autism. *J Perinat Med.* 27(6):441-50.
40. Juul-Dam N, Townsend J, Courchesne E. 2001. Prenatal, perinatal, and neonatal factors in autism, pervasive developmental disorder-not otherwise specified, and the general population. *Pediatrics.* 107(4):e63-68.
41. Wilkerson DS, Volpe AG, Dean RS, Titus JB. 2002. Perinatal complications as predictors of infantile autism. *Intern J Neuroscience.* 112:1085-1098.

42. Hultman CM, Sparen P, Cnattingius S. 2002. Perinatal risk factors for infantile autism. *Epidemiology*. 13(4);417-423.
43. Piven J, Simon J, Chase GA, Wzorek M, Landra R, et al. 1993. The etiology of autism: pre-, peri-, and neonatal factors. *J Am Acad Child Adolesc Psychiatry*. 32(6):1256-63.
44. Cryan E, Byrne M, O'Donovan A, O'Callaghan E. 1996. Brief report: a case-control study of obstetric complications and later autistic disorder. *J Aut Dev Disord*. 26(4):453-60.
45. Mason-Brothers A, Ritvo ER, Pingree C, Petersen PB, Janeson WR, et al. 1990. The UCLA-University of Utah epidemiologic survey of autism: prenatal, perinatal, and postnatal factors. *Pediatrics*. 86(4);514-19.
46. Levy S, Zoltak B, Saelens T. 1988. A comparison of obstetrical records for autistic and nonautistic referrals for psychoeducational evaluations. *J Aut Dev Disord*. 18(4):573-81.
47. Siva Subramanian KN, Yoon H, Toral JC. 2002. Extremely low birth weight infant. Available at <http://www.emedicine.com/ped/topic2784.htm>.
48. Centers for Disease Control and Prevention. 2002. Infant mortality and low birth weight among black and white infants, United States, 1980-2000. *MMWR*. 51(27):589-592.
49. Hack M, Fanaroff AA. 1999. Outcomes of children of extremely low birth weight and gestational age in the 1990s. *Early Hum Dev*. 53:193-218.
50. Halsey CL, Collin MF, Anderson CL. 1996. Extremely low birth weight children and their peers: a comparison of school-age outcomes. *Arch Pediatr Adolesc Med*. 150(8):790-4.
51. Behrman RE, Kliegman RM, Arvin AM, Nelson WE, editors. 1996. *Nelson Textbook of Pediatrics*. 15th ed. Philadelphia, PA: Saunders. 2200pp.
52. Peralta-Carcelen M, Jackson DS, Goran MI, Royal SA, Mayo MS, et al. 2000. Growth of adolescents who were born at extremely low birth weight without major disability. *J Peds*. 136(50):633-40.
53. Harvey JM, O'Callaghan MJ, Mohay H. 1999. Executive function of children with extremely low birthweight: a case control study. *Dev Med Child Neurol*. 41:292-297.
54. Peralta-Carcelen M, Hodgins B, Hart M, Nelson KG. Cognitive and behavioral function of adolescents who were born at extremely low birth weight and did not develop a major neurodevelopmental disability. Unpublished manuscript.

55. Saigal S, Rosenbaum P, Stoskopf B, Hoult L, Furlong W, et al. 1994. Comprehensive assessment of the health status of extremely low birth weight children at 8 years of age: comparison with a reference group. *J Pediatr*. 125(3):411-7.
56. Teplin SW, Burchinal M, Johnson-Martin N, Humphry RA, Kraybill EN. 1991. Neurodevelopmental, health, and growth status at age 6 years of children with birth weights less than 1001 grams. *J Pediatr*. 118(5):768-77.
57. Halsey CL, Collin MF, Anderson CL. 1993. Extremely low birth weight children and their peers: a comparison of preschool performance. *Pediatrics*. 91(4):807-11.
58. Saigal S, Szatmari P, Rosenbaum P, Campbell D, King S. 1991. Cognitive abilities and school performance of extremely low birth weight children and matched term control children at age 8 years: a regional study. *J Pediatr*. 118(5):751-60.
59. Saigal S, Stoskopf B, Streiner DL, Burrows E. 2001. Physical growth and current health status of infants who were of extremely low birth weight and controls at adolescence. *Pediatrics*. 108(2):407-415.
60. Ek U, Fernell E, Jacobson L, Gillberg C. 1998. Relation between blindness due to retinopathy of prematurity and autistic spectrum disorders: a population-based study. *Dev Med Child Neurol*. 40:297-301.
61. McEachin JJ, Smith T, Lovaas OI. 1993. Long-term outcome for children with autism who received early intensive behavioral treatment. *Am J Ment Retard*. 97(4):359-72
62. Ozonoff S, Cathcart K. 1998. Effectiveness of a home program intervention for young children with autism. *J Aut Dev Disord*. 28(1):25-32.
63. Sheinkopf SJ, Siegel B. 1998. Home-based behavioral treatment of young children with autism. *J Aut Dev Disord*. 28(1):15-23.
64. American Academy of Pediatrics. 2001. The pediatrician's role in the diagnosis and management of autistic spectrum disorder in children. *Pediatrics*. 107(5):1221-6.
65. Volkmar F, Cook EH Jr, Pomeroy J, Realmuto G, Tanguay P. 2000. Practice parameters for the assessment and treatment of children, adolescents, and adults with autism and other pervasive developmental disorders. *J Am Acad Child Adolesc Psychiatry*. 38(12):32S-54S.
66. National Research Council. 2001. *Educating Children with Autism*. Washington, DC: National Academy Press. 324 pp.

67. Riddle MA, Bernstein GA, Cook EH, Leonard HL, March JS, et al. 1999. Anxiolytics, adrenergic agents, and naltrexone. *J Am Acad Child Adolesc Psychiatry*. 38(5):546-56.
68. Gilman JT, Tuchman RF. 1995. Autism and associated behavioral disorders: pharmacotherapeutic intervention. *Ann Pharmacother*. 29(1):47-56.
69. Potenza MN, Holmes JP, Kanes SJ, McDougle CJ. 1999. Olanzapine treatment of children, adolescents, and adults with pervasive developmental disorders: an open-label pilot study. *J Clin Psychopharmacol*. 19(1):37-44.
70. Handen BL, Johnson CR, Lubetsky M. 2000. Efficacy of methylphenidate among children with autism and symptoms of attention-deficit hyperactivity disorder. *J Aut Dev Disord*. 30(3):245-55.
71. Tsai LY. 1999. Psychopharmacology in autism. *Psychosom Med*. 61(5):651-65.
72. Filipek PA, Accardo PJ, Ashwal S, Baranek GT, Cook EH, et al. 2000. Practice parameter: screening and diagnosis of autism. *Neurology*. 55(4):468-79.
73. Hyman SL, Rodier PM, Davidson P. 2001. Pervasive Developmental Disorders in Young Children. *JAMA*. 285(24):3141-2.
74. Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, et al. 2000. The Autism Diagnostic Observation Schedule-Generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Aut Dev Disord*. 30(3):205-223.
75. Krug DA, Arick JR, Almond PJ. 1980. Behavior checklist for identifying severely handicapped individuals with high levels of autistic behavior. *J Child Psychol Psychiatry*. 21(3):221-9.
76. Berument SK, Rutter M, Lord C, Pickles A, Bailey A. 1999. Autism screening questionnaire: diagnostic validity. *Br J Psychiatry*. 175:444-451.
77. Sparrow SS, Balla D, Cicchetti DV. 1984. *Vineland Adaptive Behavior Scales (Survey Form)*. Circle Pines, MN: American Guidance Services.
78. Gillham JE, Carter AS, Volkmar FR, Sparrow SS. 2000. Toward a developmental definition of autism. *J Autism Dev Disord*. 30(4):269-278.
79. Volkmar FR, Sparrow SS, Goudreau D, Cicchetti DV, Paul R, Cohen DJ. 1987. Social deficits in autism: an operational approach using the Vineland Adaptive Behavior Scales. *J Am Acad Child Adolesc Psychiatry*. 26(2):156-61.

80. Loveland KA, Kelley ML. 1991. Development of adaptive behavior in preschoolers with autism or Down syndrome. *Am J Ment Retard.* 96(1):13-20.
81. Stone WL, Ousley OY, Hepburn SL, Hogan KL, Brown CS. 1999. Patterns of adaptive behavior in very young children with autism. *Am J Ment Retard.* 104(2):187-99.
82. Palmer FB, Hoon AH. 1995. Cerebral palsy. In *Behavioral and Developmental Pediatrics*. Parker S, Zuckerman B, eds. Boston: Little, Brown & Company. 88-94.
83. Rosenhall U, Sandstrom M, Nordin V, Gillberg C. 1999. Autism and hearing loss. *J Autism Dev Disord.* 29:349-357.

APPENDIX A

DSM-IV CRITERIA FOR AUTISTIC DISORDER (299.0)

- I. A total of at least six items from (A), (B), and (C), with at least two from (A), and one each from (B) and (C)
 - A. Qualitative impairment in social interaction, as manifested by at least two of the following:
 1. marked impairments in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body posture, and gestures to regulate social interaction
 2. failure to develop peer relationships appropriate to developmental level
 3. markedly impaired expression of pleasure in other people's happiness
 4. lack of social or emotional reciprocity
 - B. Qualitative impairments in communication as manifested by at least one of the following:
 1. delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
 2. in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
 3. stereotyped and repetitive use of language or idiosyncratic language
 4. lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
 - C. Restricted repetitive and stereotyped patterns of behavior, interests and activities, as manifested by at least one of the following:
 1. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
 2. apparently inflexible adherence to specific, nonfunctional routines or rituals
 3. stereotyped and repetitive motor mannerisms (e.g. hand or finger flapping or twisting, or complex whole-body movements)
 4. persistent preoccupation with parts of objects
- II. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years:
 - A. Social interaction
 - B. Language as used in social communication
 - C. Symbolic or imaginative play
- III. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder

From the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. 1994. Washington, DC: American Psychiatric Association. 886 pp.

APPENDIX B

I. The Autism Diagnostic Observation Schedule – Generic

“The Autism Diagnostic Observation Schedule – Generic (ADOS-G), is a semi-structured assessment of social interaction, communication, play and imaginative use of materials for individuals who may have autism or other pervasive developmental disorders (PDD). As part of the schedule, planned social occasions, referred to as “presses”, are created which a range of social initiations and

responses is likely to appear. In the same way, communication opportunities are designed to elicit a range of interchanges. Play situations are included to allow observation of a range of imaginative activities and social role-play. The goal of the ADOS-G is to provide presses that elicit spontaneous behaviors in standardized contexts. Structured activities and materials, and less structured interactions, provide standard contexts within the ADOS-G in which social, communicative and other behaviors relevant to the understanding of pervasive developmental disorders are observed....

“The modules provide social-communicative sequences that combine a series of unstructured and structured situations. Each situation provides a hierarchy of presses for particular social behaviors. Module 1... is intended for children who do not use spontaneous phrase speech consistently. It consists of 10 activities with 29 accompanying ratings. Module 2 is intended for children with some flexible phrase speech who are not verbally fluent. It consists of 14 activities with 28 accompanying ratings. Module 3 provides 13 activities and 29 ratings. It is based on the ADOS and is intended for verbally fluent children for whom playing with toys is age-appropriate. The operational definition of verbal fluency is the spontaneous, flexible use of sentences, with multiple clauses that describe logical connections within a sentence. It requires the ability to talk about objects or events not immediately present. Module 4 contains the socioemotional questions of the ADOS, along with interview items about daily living and additional tasks. It is intended for verbally fluent adults and for adolescents who are not interested in playing with toys such as action figures (usually over 12-16 years). This module consists of 12-15 activities with 30 accompanying ratings.”

Cutoff scores for ADOS domains:

Module 1

Communication: autism cut-off = 4, autism spectrum cut-off = 2

Reciprocal Social Interaction: autism cut-off = 7, autism spectrum cut-off = 4

Communication + Social (Total): autism cut-off = 12, autism spectrum cut-off = 7

Module 2

Communication: autism cut-off = 5, autism spectrum cut-off = 3

Reciprocal Social Interaction: autism cut-off = 6, autism spectrum cut-off = 4

Communication + Social (Total): autism cut-off = 12, autism spectrum cut-off = 8

Module 3

Communication: autism cut-off = 3, autism spectrum cut-off = 2

Reciprocal Social Interaction: autism cut-off = 6, autism spectrum cut-off = 4

Communication + Social (Total): autism cut-off = 10, autism spectrum cut-off = 7

From Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, et al. 2000. The Autism Diagnostic Observation Schedule-Generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Aut Dev Disord.* 30(3):205-223.

II. Autism Behavior Checklist

“The Autism Behavior Checklist (ABC) is a checklist of nonadaptive behaviors, capable of providing a general picture of how an individual ‘looks’ in comparison with others. The profile of an individual’s behavior is accomplished by quantifying the behavioral characteristics on the checklist.”

Either the teacher or the parent completes the checklist, which asks questions about behaviors in five domains: sensory, relating, body and object use, language, and social and self-help. The total score, derived from the sum of scores in these five areas, is predictive of a diagnosis of autism. “An ABC score of 68 or higher has been selected as a high-probability cutoff point for the classification of autism. Scores between 54-67 fall within one standard deviation of the autistic samples studied. ABC

scores between 54-67 are considered to be in the moderate-probability range for the classification of autism. Scores between 47-53 may cause administrators confusion... Diagnosis and educational planning for these borderline individuals are greatly facilitated by administering [other tests]."

From Krug DA, Arick JR, Almond PA. 1993. *Autism Screening Instrument for Educational Planning, Second Edition: Examiner's Manual*. Austin, TX: ProEd.

III. Autism Screening Questionnaire

The Autism Screening Questionnaire (ASQ) "consists of 40 questions that are based on the ADI-R [Autism Diagnostic Interview-Revised] but which have been modified into a form understandable by parents without further explanation. These are questions on reciprocal social interaction (such as social smiling, interest in other children, and offering comfort to others), language and communication (including the use of conventional gestures, reciprocal conversation, and stereotyped utterances), and repetitive and stereotyped patterns of behaviours (including circumscribed interests and unusual preoccupations). In addition, the ASQ includes a question about self-injurious behaviour and a question about the individual's current language functioning."

"Scores of 15 or more [are suggested] as the standard optimal cut-off for differentiating PDDs (including autism) from other diagnoses. The sensitivity was 0.85, specificity 0.75, positive predictive value 0.93, and negative predictive value 0.55 [in the sample tested].... A much higher cut-off (22 or more) [are] required to separate autism from PDDs, the sensitivity being 0.75 and specificity 0.60 at that point."

From Berument SK, Rutter M, Lord C, Pickles A, Bailey A. 1999. Autism screening questionnaire: diagnostic validity. *Br J Psychiatry*. 175:444-451.

IV. Vineland Adaptive Behavior Scales

"The *Vineland Adaptive Behavior Scales*... assess personal and social sufficiency of individuals from birth to adulthood. The scales are applicable to handicapped and nonhandicapped individuals. Like the original, the revised Vineland does not require the direct administration of tasks to an individual, but instead requires a respondent who is familiar with the individual's behavior.... [The revised Vineland] measures adaptive behavior in four domains: Communication, Daily Living Skills, Socialization, and Motor Skills. In addition, [it includes] a Maladaptive Behavior domain, the administration of which is optional.

"The Survey Form, containing 297 items, provides a general assessment of adaptive behavior, which is useful for determining areas of strength and weakness. A trained interviewer administers the Survey Form to a parent of caregiver of an individual from birth to 18 years 11 months or a low-functioning adult. The semi-structured interview typically lasts between 20 and 60 minutes. The user of the Survey Form obtains norm-referenced information based on the performance of representative national standardization samples of about 4,800 handicapped and nonhandicapped individuals."

Raw scores obtained in the domains of the Vineland are then converted into standard scores according to chronological age. "Standard scores express in standard deviation units the extent to which the individual's score exceeds or falls below the mean score of persons the same age with whom the instrument was standardized.... Vineland standard scores have a mean of 100 and a standard deviation of 15."

From Sparrow SS, Balla DA, Cicchetti DV. 1984. *Vineland Adaptive Behavior Scales: Interview Edition, Survey Form Manual*. Circle Pines, MN: American Guidance Service.

**HARVEY CUSHING/JOHN HAY WHITNEY
MEDICAL LIBRARY**

MANUSCRIPT THESES

Unpublished theses submitted for the Master's and Doctor's degrees and deposited in the Medical Library are to be used only with due regard to the rights of the authors. Bibliographical references may be noted, but passages must not be copied without permission of the authors, and without proper credit being given in subsequent written or published work.

This thesis by
has been used by the following person, whose signatures attest their acceptance of the above restrictions.

NAME AND ADDRESS

DATE

YALE MEDICAL LIBRARY



3 9002 01065 6529

